

# The Head and Neck Surgeon as Clinician-Investigator

## *Opportunities and Imperatives: The Hayes Martin Lecture*

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I am honored to have been asked to present this memorial lecture in memory of Hayes Martin, MD, who is considered the father of contemporary head and neck surgery. Dr Martin was born in 1892 and died in 1977. As the chief of the head and neck surgery service at Memorial Sloan-Kettering Cancer Center, New York, New York, Dr Martin made many outstanding observations and contributions that were fundamental to the surgical management of head and neck cancer. These include the role of fine-needle aspiration biopsy for the diagnosis of solid tumors of the head and neck, management of the unknown primary, and the appropriate surgery for cervical metastasis.<sup>1</sup> Dr Martin's concepts were empirical and based on his keen observational skills and experience. He was indeed a clinician-investigator.<sup>1</sup>

In 1995, Helmuth Goepfert, MD, chairman of the Department of Head and Neck Surgery at The University of Texas MD Anderson Cancer Center, presented the Hayes Martin Lecture.<sup>2</sup> The theme of his presentation was to raise awareness of the need for the leaders in our discipline to foster the development of surgeon-scientists. He stated: "We may be training good-to-excellent clinicians, but clinical training alone is not enough to forge the future. . . . I would like to address the subject of training the head and neck surgeon/scientist of the future, for I believe we have done too little in this regard and are lagging far behind other oncologic specialties."<sup>2(p411)</sup> Dr Goepfert enumerated the qualities of such an individual, namely, one who is trained in basic science methodology, is dedicated to both patient care and scientific investigation, conducts an independent laboratory program, and is well versed in scientific methods. The surgeon-scientist creates and tests hypotheses to determine mechanisms of disease, serves as an educator and a mentor to future surgeon-scientists, and conducts research that translates laboratory discoveries to the bedside. This individual also serves as a com-

munication bridge between the PhD basic scientist and the clinician who administers care to patients with head and neck cancer.

Measures of success for surgeon-scientists are the peer-reviewed funding and leadership positions attained, a benchmark that today is aptly met in head and neck oncology. In 2009, Kupferman et al<sup>3</sup> analyzed the success of the American Head and Neck Society Research Grant Program and determined the return on investment for the \$500 000 in support provided by the society independently and in conjunction with the American Academy of Otolaryngology–Head and Neck Surgery. Most of these grants supported research conducted by surgeon-scientists and were peer reviewed. Noteworthy are the subsequent awards received by recipients of the American Head and Neck Society research grants program, which included R01s, K08s, three SPORE (Specialized Program of Research Excellence) grants, and other governmental and nongovernmental funding. On an investment of \$500 000, secondary awards to these recipients were almost \$8 million, for a return on investment of 639%. By any measure, it seems that Dr Goepfert's vision to support the development of head and neck surgeon-scientists has been re-

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alized. Examples abound of individuals in head and neck oncology who lead successful independent laboratories and multidisciplinary research programs.

In light of this success, we find ourselves at a crossroads, with the opportunity and the imperative to further foster and support head and neck surgeon clinician-investigators to take a leadership role in the future of our discipline. In Dr Drew Ridge's presidential address to the American Head and Neck Society, he eloquently presented the shortcomings of our clinical research efforts.<sup>4</sup> His address, entitled "We Show Pictures, They Show Curves," emphasized the plethora of retrospective reviews that have guided our surgical management of head and neck cancer for the past several decades. He pointed out that we have not developed a cadre of clinician-investigators to serve as leaders of clinical trials; as a result, we lack high-level data to support the role of surgery in the treatment of upper aerodigestive tract cancer. In preparing my Hayes Martin address, I reflected on the status of clinical research efforts in head and neck surgery and the future opportunities that may strengthen clinical research through our role as clinician-investigators.

*Evidence-based medicine* is defined as a set of principles and methods intended to ensure that individual medical decisions are consistent with evidence of effectiveness and benefit. The gold standard for evidence-based medicine is the prospective randomized controlled trial (RCT). In 1987, Lawrence and Mickalide<sup>5</sup> outlined the levels of clinical evidence on which clinical decisions and clinical guidelines are based. Level I, the strongest, is at least 1 RCT. Level II is divided into the following 3 sublevels: (1) controlled trials that lack randomization, (2) cohort or case-control studies, and (3) retrospective clinical reviews or analyses. Level III is consensus among respected authorities or expert opinion. Level IV represents the lowest evidence and is based on personal anecdote or experience. Much of our published data in head and neck surgery to date is based on retrospective reviews, or level II-3 evidence, rather than the more rigorous prospective RCT. Horton,<sup>6</sup> in 1996, reviewed studies published in 9 respected surgical journals reporting research. He reviewed 215 articles, of which 175 were original research reports. Of these, 46% were case series, 18% represented laboratory or animal experimentation, and only 7% reported data from an RCT. Horton stated that surgical research as a whole has been criticized for a lack of RCTs, considered the gold standard of clinical research, and for a reliance on less rigorous study designs, such as the case series. Our colleagues in other disciplines criticize surgical research for its lack of high-level evidence from RCTs.

In the development of cancer treatment guidelines, the highest-level evidence available is always cited as the preferred treatment approach. The National Comprehensive Cancer Network formulates its head and neck cancer treatment guidelines based on the highest-level evidence available. In treatment guideline development, proponents for inclusion of surgery as a treatment modality for some head and neck cancers frequently lack high-level evidence to support its inclusion.

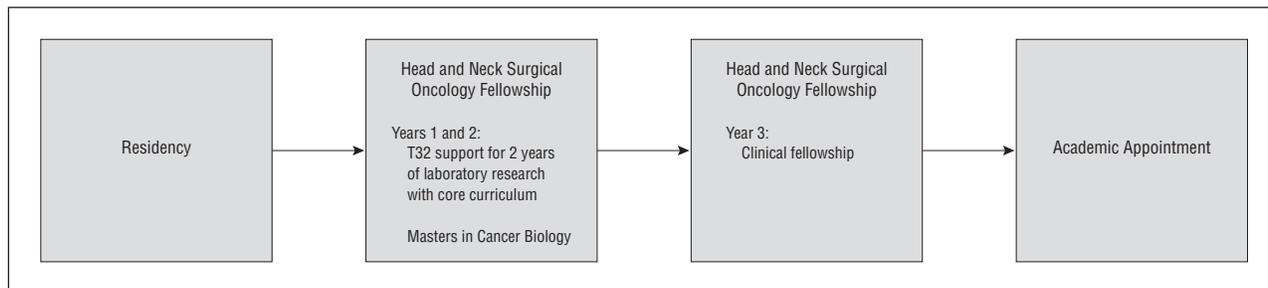
We are at a nexus of clinical research in our specialty, and many outstanding opportunities await our

trainees and young academicians as they embark on a career in head and neck surgery. I believe there are 3 overarching priorities that demand we develop competent clinician-investigators. The first priority is to create clinician-investigators who are prepared to lead clinical trials or comparative effectiveness studies that provide high-level data to better define the role of surgery and support its inclusion as part of treatment guidelines for head and neck cancer. The second priority is to train investigators who can participate in the development of personalized cancer therapy that through analysis of the patient's individual tumor will provide insight into the most appropriate administration of biological agents to disrupt the pathways leading to the phenotypic expression of cancers—specifically, uncontrolled cell division, invasion, and metastasis. The third priority is to educate investigators in the methods of health services research, quality improvement, and outcomes reporting as a means to enhance the value of health care delivery, quality, and safety.

#### CLINICIAN-INVESTIGATORS AS LEADERS OF CLINICAL TRIALS

As surgeons, our leadership in national multi-institutional head and neck cancer therapeutic trials has been limited. Advances in head and neck cancer treatment have been incremental and are due in part to well-designed clinical trials. However, with few exceptions, surgeons have participated in more of a collaborative than leadership role in these national trials. A pivotal study<sup>7</sup> led by Gregory T. Wolf, MD, and Waun Ki Hong, MD, was the initial laryngeal preservation trial that demonstrated, for the first time, that laryngeal preservation could be achieved by nonsurgical therapy without diminishing survival. In a follow-up Radiation Therapy Oncology Group study, Forastiere et al<sup>8</sup> demonstrated that patients receiving concurrent cisplatin and radiation therapy experienced a higher laryngeal preservation rate than those receiving induction chemotherapy followed by radiation therapy or radiation therapy alone. Consequently, this is the current standard of care for nonsurgical laryngeal preservation therapy. Although surgeons participated in the Radiation Therapy Oncology Group trial, the study was led by medical and radiation oncologists. Two studies,<sup>9,10</sup> one in the United States and the other in Europe, both led by radiation oncologists, demonstrated that postoperative treatment intensification with cisplatin and radiation therapy for patients with high-risk pathological findings resulted in improved disease-related outcomes. A combined analysis of these 2 studies supports the role for postoperative chemoradiotherapy in patients with positive margins or extracapsular nodal spread.<sup>11</sup> These significant postoperative trials that serve as the underpinning for current treatment guidelines were led by nonsurgeons.

At any gathering of head and neck surgeons today, one hears the lament for the diminishing role of surgery in the treatment of head and neck cancer and distress over the severe functional morbidity seen in some patients following radiation therapy or high-dose chemoradiotherapy for organ preservation. Although we tout the ad-



**Figure 1.** Sample career pathway for a clinician-investigator integrating a T32 fellowship with obtaining an MS in cancer biology.

vantages of partial laryngeal surgery over radiation therapy, we have failed to conduct an RCT comparing transoral laser microsurgery with radiation therapy for early glottic laryngeal cancer. Important outcomes of such a trial would include local control, voice quality, cost, and cancer control. Today, the introduction of new technology provides an opportunity through clinical research to reestablish surgery as an important modality for treating upper aerodigestive tract cancer.

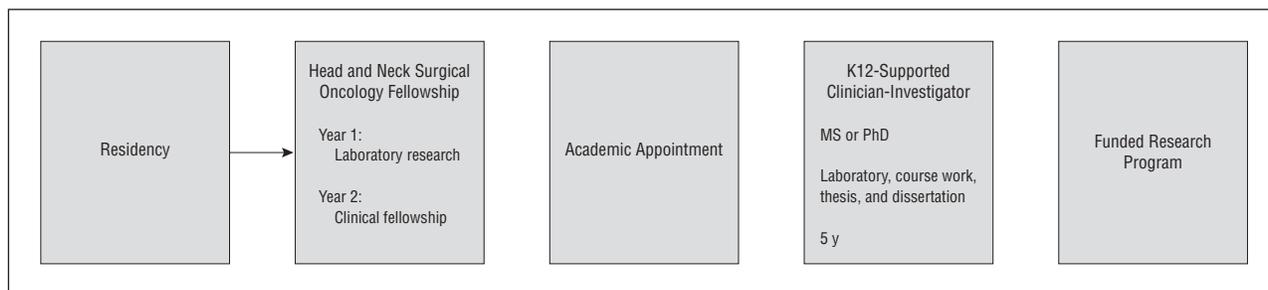
With the introduction of robotic surgery for cancers of the oropharynx and larynx, we have an outstanding opportunity to conduct an open, multicenter, nonrandomized controlled trial and registry for patients with oropharyngeal cancer. Patients would be enrolled in the registry study based on well-defined criteria for inclusion, such as tumor site and stage and risk factors. Prospective data collection would thus create a homogeneous study population. Important variables collected in a prospective manner would include disease site and stage, a cost analysis, disease-specific and overall survival, locoregional control, and functional outcome assessment through the use of validated instruments for quality-of-life and functional assessment. Critical functional end points would include the presence or absence of a tracheostomy or gastrostomy tube. Data collected from multiple institutions would serve as the basis for an evidence-based study comparing nonsurgical treatment with radiation therapy or chemoradiotherapy vs transoral robotic surgery with or without adjuvant treatment for cancers of the oropharynx. As a discipline, we need trained clinician-investigators to organize, lead, acquire resources, and ensure data quality. By seizing this and other such opportunities, surgeons as clinician-investigators may develop the evidence needed to support transoral surgery as an acceptable therapeutic option.

What have been the impediments to the development and execution of controlled trials in head and neck surgery? The reasons are multiple and include significant expense, funding resources, heterogeneity of the patient population, the reality that nominal differences in outcomes require a large sample size, defining and agreeing on end points, and variability in surgical techniques. Most important, our discipline lacks individuals who have obtained the necessary educational background and experience to design and oversee RCTs. Most large phase III trials are conducted under the auspices of the National Cancer Institute cooperative groups and are traditionally led by medical or radiation oncologists. Other impediments to trial development include the recent discontinuation of the head and neck com-

mittees of the Southwest Oncology Group and the American College of Surgeons Oncology Group. Other factors mitigating the development of head and neck surgeon clinician-investigators include education-related debt, few well-trained clinician-investigators to serve as role models and mentors, and decreasing funding opportunities, salary support, and protected time to acquire the educational prerequisites necessary to pursue this career path.

Critical to the development of the clinician-investigator is the creation of a defined educational experience emphasizing a study curriculum in the biomedical sciences leading to an MPH, an MS, or a PhD in clinical investigation. Other important elements are the institutional environment and culture. Success is dependent on a nurturing environment, available resources, cooperation among the various disciplines, mentorship, and a cultural philosophy embracing clinical research. If any of these elements is absent, the clinician-investigator, even with the appropriate prerequisites, will not succeed. Developing a new generation of clinician-investigators will require that we identify successful role models who will develop and provide a curriculum in clinical investigation and that we create intramural and extramural opportunities for clinical research. Consolidation is occurring within the cooperative groups (Eastern Cooperative Oncology Group, Radiation Therapy Oncology Group, and Cancer and Leukemia Group B) that may create new opportunities for head and neck surgeons to assume leadership roles in the development of clinical trials and to assert the inclusion of surgery as a significant therapeutic modality.

Resources exist to facilitate the development of head and neck surgeon clinician-investigators. These include the National Institutes of Health loan repayment program, T32 training grants, and the National Institutes of Health institutionally awarded K12 program that provides funding after fellowship and before the onset of a mentored K award for junior tenure-track faculty. The K12 provides salary support, allowing protected time for course work in patient-oriented research. **Figure 1** shows a career pathway of a T32 fellowship leading to the acquisition of an MS in the biological sciences. The Paul Calabresi Career Development Award in clinical oncology (K12) is designed to train clinician-investigators in the design and administration of hypothesis-based phase I, phase II, and phase III cancer therapeutic clinical trials. An important complement of the K12 award is to foster collaboration among clinical and basic research scientists that will expedite the translation of discoveries from the laboratory to the bedside. **Figure 2** shows an ex-



**Figure 2.** Sample career pathway for a clinician-investigator supported by a K12 award who is pursuing an MS or PhD to perform translational research or lead clinical trials.

**Table. Examples of Course Work Toward an MS in Cancer Biology**

<b>Epidemiology and Biostatistics</b>
Advanced epidemiology
Biostatistics for clinical investigators
Intermediate biostatistical methods 1
Intermediate biostatistical methods 2
Logistic regression analysis
Bayesian data analysis
Survival analysis
<b>Clinical Medicine</b>
Biological basis of emerging diseases
Clinical perspective of malignant disease
Principles in therapeutics
Clinical research design workshop
Design and management of clinical trials
Ethics in clinical trials research
<b>Basic Science</b>
Analysis of microarray data
Topics in molecular medicine
<b>Miscellaneous</b>
Grant and manuscript writing

ample of the career pathway for a clinician-investigator supported by a K12 award. Examples of the curriculum toward an MS for patient-oriented biological research are listed in the **Table**. These courses are the necessary prerequisites to provide a knowledge base in clinical trial design, biostatistics, bioethics, and grant and manuscript writing. The curriculum can be tailored to the prospective investigator's career pathway.

### CLINICIAN-INVESTIGATORS AND PERSONALIZED MEDICINE

If we are successful in developing head and neck surgeon clinician-investigators, we as a discipline will also be prepared to engage in the emerging field of personalized cancer therapy research. In 1971, then president Richard M. Nixon declared war on cancer. Since then, we have spent \$100 billion and have made remarkable progress toward understanding the molecular basis of cancer.<sup>12</sup> The challenge before us is to translate these discoveries into effective strategies for preventing and treating the most common cancers. Personalized therapy carries the promise to surpass the mere incremental improvement in locoregional control and survival realized through more traditional investigations.<sup>12</sup> In a meta-

analysis of 63 clinical trials evaluating the minimal absolute survival benefit for patients having head and neck cancer treated with concurrent chemoradiotherapy, Pignon et al<sup>13</sup> reported an 8% survival benefit at 5 years over those treated with induction chemotherapy and definitive radiation therapy. Bonner et al<sup>14</sup> reported an 8% improvement in locoregional control for patients treated with radiation therapy and cetuximab compared with radiation therapy alone. Most of the phase III trials evaluating new therapeutic approaches for head and neck cancer have demonstrated minimal improvement in survival and locoregional control, despite enrolling several thousand patients at great cost. These types of trials provide the best level of evidence and are designed to determine the best approach for the average population, but not for specific individuals.

The central concept of personalized medicine is selecting the right treatment for the right patient at the right time. Without a fundamental change, we will continue to see only incremental improvements and little hope for substantial survival gains. In a new era of patient-oriented research, high-throughput technologies to sequence DNA, RNA, proteins, and metabolites provide great opportunity to tailor cancer therapy at the tumor and patient levels. A revolution in technology has made this possible. It required more than a decade to sequence the human genome, at a cost of \$3 billion. In 2012, the human genome can be sequenced in 1 week for a cost of \$2000 on average.<sup>15,16</sup> The promise of this technological revolution is to provide the clinician-investigator with real-time insight into molecular aberrations specific to an individual patient's tumor. We know that cancer represents multiple distinct disease entities with varied natural history and molecular pathogenesis. We must depart from the reductionist concept of 1 target (a gene, a pathway, or a protein) attacked by 1 drug. New therapies will be combinatorial, targeting multiple receptors, proteins, genes, or pathways. Early clinical trials with targeted therapy for cancer have demonstrated several shortcomings, which include an unexpected high failure rate of molecularly targeted therapeutics, difficulty in identifying and validating molecular biomarkers, and homeostatic feedback loops and bypass mechanisms that lead to unexpected outcomes.

As we move toward personalized cancer therapy, biomarker identification will be essential for identifying likely responders and demonstrating meaningful clinical benefit, thus reducing both the number of exploratory phase II studies needed and the size of the definitive phase III

trials. Surgeons can and should take a pivotal role in the drive toward personalized care because we serve as the gatekeepers for patients with head and neck cancer. Furthermore, surgeons are able to obtain biological specimens from patients enrolled in clinical trials, which will be crucial for identifying and validating new targets. Future personalized cancer therapy will pursue a multimodal approach, including assessment of DNA, RNA, proteomics, and metabolomics, to identify the critical events for the initiation and progression of cancer. Current clinical trials with targeted agents demonstrate that a small number of patients show remarkable responses; these patients may serve as beacons if we are able to decode the underlying mechanisms responsible for this effect.<sup>17</sup> Recent discoveries have validated this approach. For example, patients having adenocarcinoma of the lung with specific epidermal growth factor receptor mutations in the catalytic domain achieve a greater clinical benefit from gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor, than those without. In melanoma, mutations of c-Kit and BRAF are functionally relevant targets for new biological agents. As more clinically relevant biomarkers are identified, clinician-investigators need to actively participate in the development of personalized care for our patients.

#### CLINICIAN-INVESTIGATORS AND HEALTH SERVICES RESEARCH

The third area of opportunity for the head and neck surgeon clinician-investigator is health services research and outcomes reporting that reflect the value, performance, and quality of care provided to patients with head and neck cancer. Health care costs are rising exponentially. It is predicted that by the middle of this century national health expenditures in the United States will exceed the gross domestic product, which is an unsustainable scenario. It is estimated that one-third of health care expenditures are wasted on care that is not evidence based, lacks proven benefit, or is harmful to the patient. Efforts to reduce the costs of health care will focus on quality, safety, efficiency, and value. The recently passed Patient Protection and Affordable Care Act<sup>18</sup> requires that by 2014 and beyond prospective payment system-exempt cancer hospitals must submit quality data. In 2012, the secretary for Health and Human Services will publish the quality and performance measures that these health care institutions must report. By 2014, the mandate is for public reporting of these outcome measures. Health and Human Services anticipates reporting quality measures that will include treatment outcomes, patient satisfaction, efficiency of care delivery, and costs of care for each hospital. With this standardization of quality control and transparency of reporting, there is an immediate need for clinician-investigators to not only establish the measures by which we will all be evaluated but also perform institutional assessments to ensure compliance with these future mandates.

Other strategies for cost reduction will focus on quality improvement and value of the care delivered. Michael Porter, an economist at Harvard Business School (Boston, Massachusetts), and his colleague Elizabeth Teis-

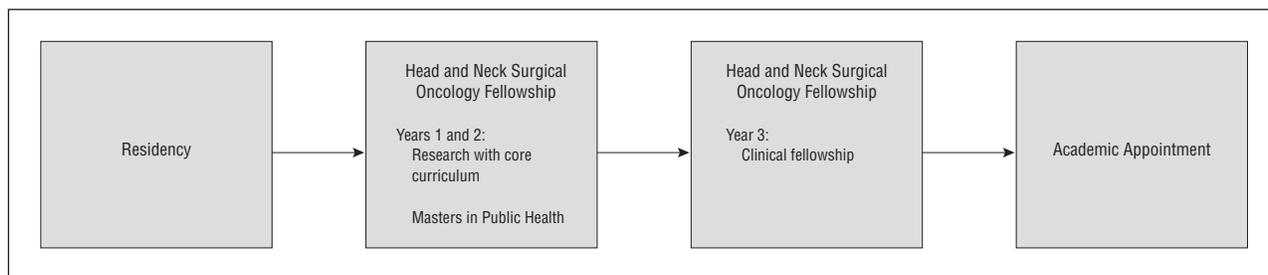
berg recently published *Redefining Health Care: Creating Value-Based Competition on Results*.<sup>19</sup> Porter and Teisberg define health care value as quality outcome divided by unit cost. In the future, institutions that demonstrate value will have a competitive advantage for outcomes-based referrals. For patients with head and neck cancer, value will be achieved by providing evidence-based treatment delivered in an efficient and cost-effective manner. In the coming era of outcomes reporting, providers and institutions that provide high-value care will benefit from access to patients directed to them by payers who seek value for their health care expenditures.

Many patients do not now receive the best evidence-based treatment for their cancer, which results in wasted resources, diminished disease control, and lower survival.<sup>20</sup> Increasingly, guideline-based therapy will serve as the basis for reimbursement by third-party payers. Failure to deliver guideline-based therapy may result in denial of charges for services rendered.

The National Comprehensive Cancer Network is composed of 44 multidisciplinary panels, with 20 to 30 disease-specific experts on each panel. Cancer treatment guidelines developed by these panels are based on level I evidence whenever possible, underscoring the importance of RCTs. Third-party payers use National Comprehensive Cancer Network guidelines for coverage policy and quality-of-care evaluation.<sup>21,22</sup> In collaboration with the National Business Group on Health (a consortium of major corporations that purchase health care coverage for their employees), the National Comprehensive Cancer Network issued a policy statement that benefit plans should provide coverage for evidence-based cancer treatment.<sup>23</sup> Clinician-investigators will have a key role by providing critical input in the development and execution of hypothesis-driven research and formulating treatment guidelines based on the results of these findings.

Investigators in the field of health services research and outcomes reporting will require, as a prerequisite, a defined curriculum to learn the methods to conduct and report these studies. The clinician-investigator pursuing a career in this area of research may choose to seek an MPH to gain the knowledge of biostatistical methods as they relate to patient populations (**Figure 3**). Other graduate courses to prepare the clinician-investigator may include integrative bioinformatics, topics in clinical cancer research and survival analysis, and health care economics. The Agency for Healthcare Research and Quality also provides a self-study program covering topics like best practices in public reporting, quality improvement support systems, and critical analyses of improvement strategies and health care efficiency measures. Regional and national symposia and colloquia provide numerous learning opportunities for young investigators in the field of health services and comparative effectiveness research.

There are many areas in which clinician-investigators can contribute to health services research. For example, one strategy for ensuring that patients receive the best available treatment for their disease is pay for performance. Providers and institutions that provide high-quality evi-



**Figure 3.** Sample career pathway for a clinician-investigator who is interested in health services research and chooses to seek an MPH.

dence-based care delivered efficiently will receive enhanced payment. Implementation of pay for performance will require health care providers and institutions to publish in the public domain their outcomes and compliance with quality measures. Recent publications have presented performance data for head and neck surgeons in an academic practice. These data, appropriately stratified for risk, procedure acuity, and comorbidity, will serve as benchmarks for head and neck surgery and comparison with other providers and institutions.<sup>24</sup>

Another area involves examining compliance with best known practices based on the best available evidence, as defined by clinical practice guidelines. As a quality measure, Hessel et al<sup>25</sup> published a study on intradepartmental compliance with accepted treatment guidelines for the management of oral tongue cancer. Although compliance with accepted treatment guidelines was high, there remained opportunities for improvement. These types of studies can serve as quality improvement tools and benchmarks for quality comparison.

In addition, providers and institutions are now reimbursed for episodes of care or procedures performed. Reimbursement schemes will likely move away from rewarding activity and toward paying for outcomes, supporting advocates who express the notion that rewarding results is paramount. An emerging strategy for reduction of health care expenditures is new payment methods. An area targeted for cost reduction is the traditional fee-for-service model. One proposal is the implementation of a bundled payment system.<sup>26</sup> Analogous to the diagnosis-related-group payment scheme for inpatient services, a bundled payment system would provide a global payment for a disease entity. An example would be a patient with stage II oral tongue cancer requiring a diagnostic evaluation, surgical treatment, and possibly radiation therapy as an adjunct to surgery. One payment would be provided to cover the costs of care related to the patient's cancer diagnoses. In a bundled payment environment, the provider takes on the risk of delivering care that is cost-effective, is efficient, and avoids waste. Failure to do so would result in significant financial risk to the health care organization. Accurately establishing the true cost of the care provided and the effect of comorbidity and complications on the overall costs will be an imperative for maintaining financial viability. This creates opportunities for the clinician-investigator trained in health services research and health care economics to participate in the analysis of the cost of care within a practice unit and institution.

## CONCLUSIONS

This is a time of great opportunities and imperatives for head and neck oncology. The 3 career pathways discussed herein lie ahead for clinician-investigators and hold promise for the future of our discipline. Increasingly, head and neck cancer treatment will be based on guidelines supported by evidence from prospective clinical trials. We must foster the education and academic development of surgeons who will become adept at developing and leading hypothesis-driven clinical trials that will define the role for surgery in the multidisciplinary management of head and neck cancer. We must develop a cadre of clinician-investigators educated in the biological basis for cancer development and progression, who as translational scientists will participate in the evolution of personalized cancer therapy. Finally, as greater emphasis is placed on health care quality, value, safety, and efficiency as a means to reduce health care expenditures, clinician-investigators with training in health services research and outcomes reporting will find great opportunities for academic development, while improving the care we provide for our patients with head and neck cancer.

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## REFERENCES

1. Helsper JT. Hayes Martin, MD: an exemplary heritage. *Arch Otolaryngol Head Neck Surg.* 2005;131(7):561-563.
2. Goepfert H. Hayes Martin Lecture. Training the head and neck surgeon-scientist. *Am J Surg.* 1995;170(5):410-415.

3. Kupferman ME, Moskovic DJ, Weber RS, Boyle J. Better than Buffett?: a report on the success of the American Head and Neck Society Research Grant Program. *Arch Otolaryngol Head Neck Surg.* 2009;135(11):1082-1086.
4. Ridge JA. We show pictures, they show curves. *Arch Otolaryngol Head Neck Surg.* 2010;136(12):1170-1175.
5. Lawrence RS, Mickalide AD. Preventive services in clinical practice: designing the periodic health examination. *JAMA.* 1987;257(16):2205-2207.
6. Horton R. Surgical research or comic opera: questions, but few answers. *Lancet.* 1996;347(9007):984-985.
7. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med.* 1991;324(24):1685-1690.
8. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *N Engl J Med.* 2003;349(22):2091-2098.
9. Cooper JS, Pajak TF, Forastiere AA, et al; Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
10. Bernier J, Dommene C, Ozsahin M, et al; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.
11. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck.* 2005;27(10):843-850.
12. Potti A, Schilsky RL, Nevins JR. Refocusing the war on cancer: the critical role of personalized treatment. *Sci Transl Med.* 2010;2(28):cm13. <http://stm.sciencemag.org/content/2/28/28cm13.full.pdf>. Accessed February 27, 2011.
13. Pignon JP, Bourhis J, Dommene C, Designé L; MACH-NC Collaborative Group; Meta-Analysis of Chemotherapy on Head and Neck Cancer. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. *Lancet.* 2000;355(9208):949-955.
14. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2006;354(6):567-578.
15. Cronin M, Ross JS. Comprehensive next-generation cancer genome sequencing in the era of targeted therapy and personalized oncology. *Biomark Med.* 2011;5(3):293-305.
16. Pareek CS, Smoczynski R, Tretyan A. Sequencing technologies and genome sequencing [published online ahead of print June 23, 2011]. *J Appl Genet.* doi:10.1007/s13353-011-0057-x.
17. Gonzalez-Angulo AM, Hennessy BT, Mills GB. Future of personalized medicine in oncology: a systems biology approach. *J Clin Oncol.* 2010;28(16):2777-2783.
18. Patient Protection and Affordable Care Act. Pub L No. 111-148, HR 3590.
19. Porter ME, Teisberg EO. *Redefining Health Care: Creating Value-Based Competition on Results.* Boston, MA: Harvard Business Press; 2006.
20. Lewis CM, Hessel AC, Roberts DB, et al. Prereferral head and neck cancer treatment: compliance with national comprehensive cancer network treatment guidelines. *Arch Otolaryngol Head Neck Surg.* 2010;136(12):1205-1211.
21. Rodgers GM. Guidelines for the use of erythropoietic growth factors in patients with chemotherapy-induced anemia. *Oncology (Williston Park).* 2006;20(8)(suppl 6):12-15.
22. Johnson PE, Dahlman G, Eng K, et al; NCCN Oncology Risk Evaluation and Mitigation Strategies (REMS) Work Group. NCCN Oncology Risk Evaluation and Mitigation Strategies white paper: recommendations for stakeholders. *J Natl Compr Canc Netw.* 2010;8(suppl 7):S7-S27.
23. Danielson E, Goldsmith PJ. Access to cancer care in the era of restricted provider networks. *J Natl Compr Canc Netw.* 2010;8(9):967.
24. Weber RS, Lewis CM, Eastman SD, et al. Quality and performance indicators in an academic department of head and neck surgery. *Arch Otolaryngol Head Neck Surg.* 2010;136(12):1212-1218.
25. Hessel AC, Moreno MA, Hanna EY, et al. Compliance with quality assurance measures in patients treated for early oral tongue cancer. *Cancer.* 2010;116(14):3408-3416.
26. Evans J. Bundled payment: a promising initiative of payment reform. *Am Health Drug Benefits.* 2010;3(3):189-190.